

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NICARDIPINE HYDROCHLORIDE safely and effectively. See full prescribing information for NICARDIPINE HYDROCHLORIDE.

NICARDIPINE HYDROCHLORIDE injection for intravenous use
Initial U.S. Approval: 1988

INDICATIONS AND USAGE

- Nicardipine hydrochloride injection is a calcium channel blocker indicated for the short-term treatment of hypertension when oral therapy is not feasible.

DOSAGE AND ADMINISTRATION

- For Intravenous Use.
- DILUTE VIALS BEFORE INFUSION (2.2).
- Individualize dosage based upon the severity of hypertension and response of the patient during dosing (2.1).
- When substituting for oral nicardipine therapy, use the intravenous infusion rate from the table to produce an average plasma concentration equivalent to a given oral dose at steady state (2.3):

| Oral Nicardipine Dose | Equivalent I.V. Infusion Rate |
|-----------------------|-------------------------------|
| 20 mg q8h | 0.5 mg/hr |
| 30 mg q8h | 1.2 mg/hr |
| 40 mg q8h | 2.2 mg/hr |

- In a drug-free patient, initiate therapy at 50 mL/hr (5 mg/hr). For gradual reduction in blood pressure, increase the infusion rate by 25 mL/hr every 15 minutes up to a maximum of 150 mL/hr until desired blood pressure reduction is achieved. For rapid blood pressure reduction, increase the infusion rate by 25 mL/hr every 5 minutes up to a maximum of 150 mL/hr (2.4).
- If unacceptable hypotension or tachycardia ensues, discontinue the infusion. When blood pressure and heart rate stabilize, restart the infusion at low doses such as 30-50 mL/hr (2.5).

DOSAGE FORMS AND STRENGTHS

- 25 mg /10 mL solution in a single-use vial for intravenous administration (3)

CONTRAINDICATIONS

- Do not use in patients with advanced aortic stenosis (4.1).

WARNINGS AND PRECAUTIONS

- To reduce the possibility of venous thrombosis, phlebitis, and vascular impairment, do not use small veins, such as those on the dorsum of the hand or wrist. Exercise extreme care to avoid intra-arterial administration or extravasation (5.7).
- To minimize the risk of peripheral venous irritation, change the site of infusion of nicardipine every 12 hours (5.7).
- Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal. Withdraw beta-blockers gradually (5.8).
- Closely monitor response in patients with angina (5.3), congestive heart failure (5.4), impaired hepatic function (5.5), portal hypertension (5.5), and renal impairment (5.6) and pheochromocytoma (5.9).

ADVERSE REACTIONS

Most common adverse reactions are headache (13%), hypotension (5%), tachycardia (4%) and nausea/vomiting (4%).

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA at 1-888-838-2872 x 6351 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Cimetidine increases nicardipine plasma levels (7.3).
- Nicardipine increases cyclosporine plasma levels. Monitor cyclosporine levels when co-administering with nicardipine (7.5).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing Mothers: It is recommended that women who wish to breastfeed should not be given this drug (8.3).
- Safety and efficacy in patients under the age of 18 have not been established (8.4).

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypertension

Nicardipine hydrochloride injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits [*see Dosage and Administration (2.6)*].

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Nicardipine hydrochloride injection is intended for intravenous use. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing. Blood pressure and heart rate should be monitored both during and after the infusion to avoid tachycardia or too rapid or excessive reduction in either systolic or diastolic blood pressure.

2.2 Preparation

Warning: Dilute vials before infusion.

Dilution

Nicardipine hydrochloride injection is administered by slow continuous infusion at a CONCENTRATION OF 0.1 MG/ML. Each vial (25 mg) should be diluted with 240 mL of compatible intravenous fluid (see below), resulting in 250 mL of solution at a concentration of 0.1 mg/mL.

Nicardipine hydrochloride injection has been found compatible and stable in polyvinyl chloride containers for 24 hours at controlled room temperature with:

Dextrose (5%) Injection, USP

Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP

Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP

Dextrose (5%) with 40 mEq Potassium, USP

Sodium Chloride (0.45%) Injection, USP

Sodium Chloride (0.9%) Injection, USP

Nicardipine hydrochloride injection is *not* compatible with Sodium Bicarbonate (5%) Injection, USP or Lactated Ringer's Injection, USP.

The diluted solution is stable for 24 hours at room temperature.

Inspection

Visually inspect nicardipine hydrochloride injection for particulate matter and discoloration prior to administration, whenever solution and container permit. Nicardipine hydrochloride injection is normally light yellow in color.

2.3 Dosage as a Substitute for Oral Nicardipine Therapy

The intravenous infusion rate required to produce an average plasma concentration equivalent to a given oral dose at steady state is shown in the following table:

| Oral Nicardipine Dose | Equivalent I.V. Infusion Rate |
|-----------------------|-------------------------------|
| 20 mg q8h | 0.5 mg/hr |
| 30 mg q8h | 1.2 mg/hr |
| 40 mg q8h | 2.2 mg/hr |

2.4 Dosage for Initiation of Therapy in a Drug-Free Patient

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. Nicardipine hydrochloride injection is administered by slow continuous infusion at a concentration of 0.1 mg/mL. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes. When treating acute hypertensive episodes in patients with chronic hypertension, discontinuation of infusion is followed by a 50% offset of action in 30 ± 7 minutes but plasma levels of drug and gradually decreasing antihypertensive effects exist for many hours.

Titration

For a gradual reduction in blood pressure, initiate therapy at a rate of 50 mL/hr (5 mg/hr). If desired blood pressure reduction is not achieved at this dose, increase the infusion rate by 25 mL/hr (2.5 mg/hr) every 15 minutes up to a maximum of 150 mL/hr (15 mg/hr), until desired blood pressure reduction is achieved. For more rapid blood pressure reduction, titrate every 5 minutes.

Maintenance

Adjust the rate of infusion as needed to maintain desired response.

2.5 Conditions Requiring Infusion Adjustment

Hypotension or Tachycardia: In case of hypotension or tachycardia, discontinue infusion. When blood pressure and heart rate stabilize, restart infusion at low doses such as 30-50 mL/hr (3-5 mg/hr) and titrate to maintain desired blood pressure.

Infusion Site Changes: Change infusion site every 12 hours if administered via peripheral vein.

Impaired Cardiac, Hepatic, or Renal Function: Monitor closely when titrating nicardipine hydrochloride injection in patients with congestive heart failure or impaired hepatic or renal function [see *Warnings and Precautions* (5.4, 5.5 and 5.6)].

2.6 Transfer to Oral Antihypertensive Agents

If treatment includes transfer to an oral antihypertensive agent other than nicardipine capsules, initiate oral therapy upon discontinuation of nicardipine hydrochloride injection.

When switching to a TID regimen of nicardipine capsules, administer the first dose 1 hour prior to discontinuation of the infusion.

3 DOSAGE FORMS AND STRENGTHS

Single-use amber glass vials contain 25 mg of 2.5 mg/mL solution for intravenous injection.

4 CONTRAINDICATIONS

4.1 Advanced Aortic Stenosis

Do not use nicardipine in patients with advanced aortic stenosis because of the afterload reduction effect of nicardipine. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

5 WARNINGS AND PRECAUTIONS

5.1 Excessive Pharmacologic Effects

In administering nicardipine, close monitoring of blood pressure and heart rate is required. Nicardipine may occasionally produce symptomatic hypotension or tachycardia. Avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

5.2 Rapid Decreases in Blood Pressure

No clinical events have been reported suggestive of a too rapid decrease in blood pressure with nicardipine. However, as with any antihypertensive agent, blood pressure lowering should be accomplished over as long a time as is compatible with the patient's clinical status.

5.3 Use in Patients with Angina

Increases in frequency, duration, or severity of angina have been seen in chronic oral therapy with nicardipine capsules. Induction or exacerbation of angina has been seen in less than 1% of coronary artery disease patients treated with nicardipine. The mechanism of this effect has not been established.

5.4 Use in Patients with Congestive Heart Failure

Nicardipine reduced afterload without impairing myocardial contractility in preliminary hemodynamic studies of CHF patients. However, *in vitro* and in some patients, a negative inotropic effect has been observed. Therefore, monitor vital signs carefully when using nicardipine, particularly in combination with a beta-blocker, in patients with CHF or significant left ventricular dysfunction.

5.5 Use in Patients with Impaired Hepatic Function

Since nicardipine is metabolized in the liver, consider lower dosages and closely monitor response. Nicardipine administered intravenously increased hepatic venous pressure gradient by 4 mmHg in cirrhotic patients at high doses (5 mg/20 min) in one study. Use caution in patients with portal hypertension.

5.6 Use in Patients with Impaired Renal Function

When nicardipine was given to mild-to-moderate hypertensive patients with moderate renal impairment, a significantly lower systemic clearance and higher AUC was observed. These results are consistent with those seen after oral administration of nicardipine. Careful dose titration is advised when treating patients with more than mild renal impairment.

5.7 Intravenous Infusion Site

To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, extravasation, and the rare occurrence of vascular impairment, administer drug through large peripheral veins or central veins rather than arteries or small peripheral veins, such as those on the dorsum of the hand or wrist. To minimize the risk of peripheral venous irritation, consider changing the site of the drug infusion every 12 hours.

5.8 Beta-Blocker Withdrawal

Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal. Withdraw beta-blockers gradually.

5.9 Use in Patients with Pheochromocytoma

Only limited clinical experience exists in use of nicardipine for patients with hypertension from pheochromocytoma.

6 ADVERSE REACTIONS

6.1 Adverse Reactions Observed in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Two hundred forty-four patients participated in two multicenter, double-blind, placebo-controlled trials of nicardipine. Adverse experiences were generally not serious and most were expected consequences of vasodilation. Adverse reactions occasionally required dosage adjustment. Therapy was discontinued in approximately 12% of patients, mainly due to hypotension, headache, and tachycardia. Adverse reactions that occurred more often on nicardipine than on placebo by at least 2% were headache (13%) and nausea/vomiting (4%).

The following adverse reactions have been reported in clinical trials or in the literature during the use of intravenously administered nicardipine.

Body as a Whole: fever, neck pain

Cardiovascular: angina pectoris, atrioventricular block, ST segment depression, inverted T wave, deep-vein thrombophlebitis

Digestive: dyspepsia

Hemic and Lymphatic: thrombocytopenia

Metabolic and Nutritional: hypophosphatemia, peripheral edema

Nervous: confusion, hypertonia

Respiratory: respiratory disorder

Special Senses: conjunctivitis, ear disorder, tinnitus

Urogenital: urinary frequency

Sinus node dysfunction and myocardial infarction, which may be due to disease progression, have been seen in patients on chronic therapy with orally administered nicardipine.

7 DRUG INTERACTIONS

7.1 Antihypertensive Agents

Since nicardipine hydrochloride injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and to treat promptly any undesired effects from concomitant administration.

7.2 Beta-Blockers

In most patients, nicardipine hydrochloride injection can safely be used concomitantly with beta-blockers. However, monitor response carefully when combining nicardipine hydrochloride injection with a beta-blocker in the treatment of congestive heart failure patients [see *Warnings and Precautions* (5.4)].

7.3 Cimetidine

Cimetidine has been shown to increase nicardipine plasma concentrations with oral nicardipine administration. Carefully monitor patients receiving the two drugs concomitantly. Data with other histamine-2 antagonists are not available.

7.4 Digoxin

Studies have shown that oral nicardipine usually does not alter digoxin plasma concentrations.

7.5 Cyclosporine

Concomitant administration of oral nicardipine and cyclosporine results in elevated plasma cyclosporine levels. Monitor closely plasma concentrations of cyclosporine during nicardipine hydrochloride injection administration, and adjust the dose of cyclosporine accordingly.

7.6 In Vitro Interaction

The plasma protein binding of nicardipine was not altered when therapeutic concentrations of furosemide, propranolol, dipyridamole, warfarin, quinidine, or naproxen were added to human plasma *in vitro*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of nicardipine use in pregnant women. There are limited human data in pregnant women with pre-eclampsia and preterm labor. In animal reproduction and developmental toxicity studies, evidence of fetal harm was observed. Therefore use nicardipine during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproduction studies conducted in rats and rabbits, increased embryoletality occurred when nicardipine was administered intravenously at doses equivalent to human IV doses of 1.6 mg/kg/day (rats) and 0.32 mg/kg/day (rabbits).

Increased embryoletality was also observed when nicardipine was administered orally to pregnant rabbits at a dose equivalent to a human oral dose of about 48 mg/kg/day (a dose 24 times the maximum recommended human oral dose and one associated with marked maternal body weight gain suppression). At a lower oral dose, equivalent to a human dose of about 32 mg/kg/day (16 times the maximum recommended human oral dose), in a different strain of rabbit, there were no adverse effects on the fetus, though there was increased maternal mortality. There was no evidence of embryoletality or teratogenicity when pregnant rats were administered nicardipine orally at a dose equivalent to a human oral dose of about 16 mg/kg/day (8 times the MRHD); however, dystocia, reduced birth weight, reduced neonatal survival and reduced neonatal weight gain were reported [see *Nonclinical Toxicology* (13.3)].

8.3 Nursing Mothers

Nicardipine is minimally excreted into human milk. Among 18 infants exposed to nicardipine through breast milk in the postpartum period, calculated daily infant dose was less than 0.3 mcg and there were no adverse events observed. It is recommended that women who wish to breastfeed should not be given this drug.

In a study of 11 women who received oral nicardipine 4 to 14 days postpartum, 4 women received immediate-release nicardipine 40 to 80 mg daily, 6 received sustained-release nicardipine 100 to 150 mg daily, and one received intravenous nicardipine 120

mg daily. The peak milk concentration was 7.3 mcg/L (range 1.9-18.8), and the mean milk concentration was 4.4 mcg/L (range 1.3-13.8). Infants received an average of 0.073% of the weight-adjusted maternal oral dose and 0.14% of the weight-adjusted maternal intravenous dose.

In another study of seven women who received intravenous nicardipine for an average of 1.9 days in the immediate postpartum period as therapy for pre-eclampsia, 34 milk samples were obtained at unspecified times and nicardipine was undetectable (<5 mcg/L) in 82% of the samples. Four women who received 1 to 6.5 mg/hour of nicardipine had 6 milk samples with detectable nicardipine levels (range 5.1 to 18.5 mcg/L). The highest concentration of 18.5 mcg/L was found in a woman who received 5.5 mg/hour of nicardipine. The estimated maximum dose in a breastfed infant was < 0.3 mcg daily or between 0.015 to 0.004% of the therapeutic dose in a 1 kg infant.

8.4 Pediatric Use

Safety and efficacy in patients under the age of 18 have not been established.

8.5 Geriatric Use

The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (>65 years) and young healthy adults. Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and concomitant disease of other drug therapy.

10 OVERDOSAGE

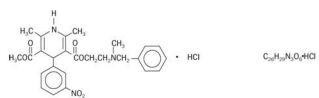
Several overdosages with orally administered nicardipine have been reported. One adult patient allegedly ingested 600 mg of nicardipine immediate release capsules, and another patient, 2160 mg of the sustained release formulation of nicardipine. Symptoms included marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion and slurred speech. All symptoms resolved without sequelae. An overdosage occurred in a one-year-old child who ingested half of the powder in a 30 mg nicardipine standard capsule. The child remained asymptomatic.

Based on results obtained in laboratory animals, lethal overdose may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdosage, standard measures including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned to avoid cerebral anoxia. Frequent blood pressure determinations are essential. Vasopressors are clinically indicated for patients exhibiting profound hypotension. Intravenous calcium gluconate may help reverse the effects of calcium entry blockade.

11 DESCRIPTION

Nicardipine hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker). Nicardipine hydrochloride for intravenous administration contains 2.5 mg/mL of nicardipine hydrochloride. Nicardipine hydrochloride is a dihydropyridine derivative with IUPAC (International Union of Pure and Applied Chemistry) chemical name (±)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2, 6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride and has the following structure:



Nicardipine hydrochloride is a yellow to pale yellow, odorless, crystalline powder that has a melting point range of 165-170° C. It is soluble in methanol, sparingly soluble in ethanol, slightly soluble in acetone, chloroform and water. It has a molecular weight of 515.99.

Nicardipine hydrochloride injection is available as a sterile, non-pyrogenic, clear, yellow solution in 10 mL vials for intravenous infusion after dilution. Each mL contains 2.5 mg nicardipine hydrochloride, 0.305 mg benzoic acid, USP and 7.5 mg sodium chloride, USP, in Water for Injection, USP. Sodium hydroxide, NF, may have been added to adjust pH to 3.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nicardipine inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine produced relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

12.2 Pharmacodynamics

Hemodynamics

Nicardipine produces significant decreases in systemic vascular resistance. In a study of intra-arterially administered nicardipine, the degree of vasodilation and the resultant decrease in blood pressure were more prominent in hypertensive patients than in normotensive volunteers. Administration of nicardipine to normotensive volunteers at dosages of 0.25 to 3 mg/hr for eight hours produced changes of <5 mmHg in systolic blood pressure and <3 mmHg in diastolic blood pressure.

An increase in heart rate is a normal response to vasodilation and decrease in blood pressure; in some patients these increases in heart rate may be pronounced. In placebo-controlled trials, the mean increases in heart rate were 7 ± 1 bpm in postoperative patients and 8 ± 1 bpm in patients with severe hypertension at the end of the maintenance period.

Hemodynamic studies following intravenous dosing in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in ejection fraction and cardiac output with no significant change, or a small decrease, in left ventricular end-diastolic pressure (LVEDP). There is evidence that nicardipine increases blood flow. Coronary dilatation induced by nicardipine improves perfusion and aerobic metabolism in areas with chronic ischemia, resulting in reduced lactate production and augmented oxygen consumption. In patients with coronary artery disease, nicardipine, administered after beta-blockade, significantly improved systolic and diastolic left ventricular function.

In congestive heart failure patients with impaired left ventricular function, nicardipine increased cardiac output both at rest and during exercise. Decreases in left ventricular end-diastolic pressure were also observed. However, in some patients with severe left ventricular dysfunction, it may have a negative inotropic effect and could lead to worsened failure.

"Coronary steal" has not been observed during treatment with nicardipine (Coronary steal is the detrimental redistribution of coronary blood flow in patients with coronary artery disease from under-perfused areas toward better perfused areas.) Nicardipine has been shown to improve systolic shortening in both normal and hypokinetic segments of myocardial muscle. Radionuclide angiography has confirmed that wall motion remained improved during increased oxygen demand. (Occasional patients have developed increased angina upon receiving nicardipine capsules. Whether this represents coronary steal in these patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.)

In patients with coronary artery disease, nicardipine improves left ventricular diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously underperfused areas. There is little or no effect on normal myocardium, suggesting the improvement is mainly by indirect mechanisms such as afterload reduction and reduced ischemia. Nicardipine has no negative effect on myocardial relaxation at therapeutic doses. The clinical benefits of these properties have not yet been demonstrated.

Electrophysiologic Effects

In general, no detrimental effects on the cardiac conduction system have been seen with nicardipine. During acute electrophysiologic studies, it increased heart rate and prolonged the corrected QT interval to a minor degree. It did not affect sinus node recovery or SA conduction times. The PA, AH, and HV intervals or the functional and effective refractory periods of the atrium were not prolonged. The relative and effective refractory periods of the His-Purkinje system were slightly shortened.

Hepatic Function

Because nicardipine is extensively metabolized by the liver, plasma concentrations are influenced by changes in hepatic function. In a clinical study with nicardipine capsules in patients with severe liver disease, plasma concentrations were elevated and the half-life was prolonged [see *Warnings and Precautions* (5.5)]. Similar results were obtained in patients with hepatic disease when nicardipine hydrochloride was administered for 24 hours at 0.6 mg/hr.

Renal Function

When nicardipine was given to mild-to-moderate hypertensive patients with moderate degrees of renal impairment, significant reduction in glomerular filtration rate (GFR) and effective renal plasma flow (RPF) were observed. No significant differences in liver blood flow were observed in these patients. A significantly lower systemic clearance and higher area under the curve (AUC) were observed.

When nicardipine capsules (20 mg or 30 mg TID) were given to hypertensive patients with impaired renal function, mean plasma concentrations, AUC, and C_{\max} were approximately two-fold higher than in healthy controls. There was a transient increase in electrolyte excretion, including sodium [see *Warnings and Precautions* (5.6)].

Acute bolus administration of nicardipine hydrochloride injection (2.5 mg) in healthy volunteers decreased mean arterial pressure and renal vascular resistance; glomerular filtration rate (GFR), renal plasma flow (RPF), and the filtration fraction were unchanged. In healthy patients undergoing abdominal surgery, nicardipine hydrochloride injection (10 mg over 20 minutes) increased GFR with no change in RPF when compared with placebo. In hypertensive type II diabetic patients with nephropathy, nicardipine capsules (20 mg TID) did not change RPF and GFR, but reduced renal vascular resistance.

Pulmonary Function

In two well-controlled studies of patients with obstructive airway disease treated with nicardipine capsules, no evidence of increased bronchospasm was seen. In one of the studies, nicardipine capsules improved forced expiratory volume 1 second (FEV₁) and forced vital capacity (FVC) in comparison with metoprolol. Adverse reactions reported in a limited number of patients with asthma, reactive airway disease, or obstructive airway disease were similar to reactions in other patients treated with nicardipine capsules.

12.3 Pharmacokinetics

Distribution

A rapid dose-related increase in nicardipine plasma concentrations is seen during the first two hours after the start of an infusion of nicardipine. Plasma concentrations increase at a much slower rate after the first few hours, and approach steady state at 24 to 48 hours. The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (>65 years) and young healthy adults. On termination of the infusion, nicardipine concentrations decrease rapidly, with at least a 50% decrease during the first two hours post-infusion. The effects of nicardipine on blood pressure significantly correlate with plasma concentrations. Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range.

Following infusion, nicardipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase (α -half-life of 3 minutes), an intermediate phase (β -half-life of 45 minutes), and a slow terminal phase (γ -half-life of 14 hours) that can only be detected after long-term infusions. Total plasma clearance (Cl) is 0.4 L/hr·kg, and the apparent volume of distribution (V_d) using a non-compartment model is 8.3 L/kg. The pharmacokinetics of nicardipine is linear over the dosage range of 0.5 to 40 mg/hr.

Metabolism and Excretion

Nicardipine has been shown to be rapidly and extensively metabolized by the liver. Nicardipine does not induce or inhibit its own metabolism and does not induce or inhibit hepatic microsomal enzymes.

After coadministration of a radioactive intravenous dose of nicardipine with an oral 30 mg dose given every 8 hours, 49% of the radioactivity was recovered in the urine and 43% in the feces within 96 hours. None of the dose was recovered as unchanged nicardipine.

*PA = conduction time from high to low right atrium; AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time; HV = conduction time through the His bundle and the bundle branch-Purkinje system.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of 5, 15, or 45 mg/kg/day) for two years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One- and three-month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid.

In rats on an iodine deficient diet, nicardipine administration for one month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes. There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for one year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (human equivalent dose about 16 mg/kg/day, 8 times the maximum recommended human oral dose).

13.3 Reproductive and Developmental Toxicology

Embryolethality, but no teratogenicity, was seen at intravenous doses of 10 mg nicardipine/kg/day in rats and 1 mg/kg/day in rabbits. These doses in the rat and rabbit are equivalent to human IV doses of about 1.6 mg/kg/day and 0.32 mg/kg/day, respectively. (The

total daily human dose delivered by a continuous IV infusion ranges from 1.2 to 6 mg/kg/day, depending on duration at different infusion rates ranging from 3 to 15 mg/hr as individual patients are titrated for optimal results.) Nicardipine was also embryocidal when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe), but not at 50 mg/kg/day (human equivalent dose about 16 mg/kg/day or about 8 times the maximum recommended human oral dose). No adverse effects on the fetus were observed when New Zealand albino rabbits were treated orally, during organogenesis, with up to 100 mg nicardipine/kg/day (a dose associated with significant mortality in the treated doe). In pregnant rats administered nicardipine orally at doses of up to 100 mg/kg/day (human equivalent dose about 16 mg/kg/day) there was no evidence of embryoletality or teratogenicity. However, dystocia, reduced birth weight, reduced neonatal survival and reduced neonatal weight gain were noted.

14 CLINICAL STUDIES

Effects in Hypertension

In patients with mild-to-moderate chronic stable essential hypertension, nicardipine hydrochloride injection (0.5 to 4 mg/hr) produced dose-dependent decreases in blood pressure, although only the decreases at 4 mg/hr were statistically different from placebo. At the end of a 48-hour infusion at 4 mg/hr, the decreases were 26 mmHg (17%) in systolic blood pressure and 21 mmHg (20%) in diastolic blood pressure. In other settings (e.g., patients with severe or postoperative hypertension), nicardipine hydrochloride injection (5 to 15 mg/hr) produced dose-dependent decreases in blood pressure. Higher infusion rates produced therapeutic responses more rapidly. The mean time to therapeutic response for severe hypertension, defined as diastolic blood pressure \leq 95 mmHg or \geq 25 mmHg decrease and systolic blood pressure \leq 160 mmHg, was 77 ± 5 minutes. The average maintenance dose was 8.0 mg/hr. The mean time to therapeutic response for postoperative hypertension, defined as \geq 15% reduction in diastolic or systolic blood pressure, was 12 minutes. The average maintenance dose was 3 mg/hr.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

Nicardipine hydrochloride injection is available in packages as follows:

| NDC | Strength | Packaged |
|--------------|-----------------------------------|-------------------|
| 0703-8315-03 | 25 mg Single-Use Vial (2.5 mg/mL) | 10 vials of 10 mL |

16.2 Storage and Handling

Store at controlled room temperature 20° to 25°C (68° to 77°F), refer to USP Controlled Room Temperature.

Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided. Protect from light. Store vials in carton until used.

17 PATIENT COUNSELING INFORMATION

Nicardipine hydrochloride injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or desirable. For prolonged control of blood pressure, patients should be transferred to oral medication as soon as their clinical condition permits. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

Blood pressure and heart rate should be monitored both during and after the infusion; too rapid or excessive reduction in either systolic or diastolic blood pressure or tachycardia during parenteral treatment should be avoided.

For treatment of overdosage, standard measures including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned to avoid cerebral anoxia.

Manufactured by:

Teva Parenteral Medicines, Inc.

Irvine, CA 92618

PRINCIPAL DISPLAY PANEL - 25 mg vial label

NDC 0703-8315-03

Rx only

Nicardipine

Hydrochloride Injection

25 mg/10 mL



(2.5 mg/mL)

Single-Use Vials

WARNING: MUST BE DILUTED BEFORE INFUSION

10 Vials

TEVA

| | | |
|---|-------------|---|
| MOC 0703-8315-03 | 15 each | Each 10 mL vial contains 25 mg nicardipine hydrochloride, 3.65 mg benzoic acid, USP and 75 mg sodium chloride, USP. Water for Injection, USP Sodium hydroxide may have been added to adjust pH to 3.5. |
| <p align="center">Nicardipine</p> | | |
| <p align="center">Hydrochloride Injection</p> | | |
| <p align="center">25 mg/10 mL</p> | | |
| Single-Dose Vials WARNING: MUST BE DILUTED BEFORE INFUSION 10 Vials | (2.5 mg/mL) | Store at 20°-25°C (68°-77°F) (See USP) Protect from light. Store in a carton until ready to use. Usual Dosage: See Package Insert. Iava Parenteral Medicines, Inc. Irvine, CA 92618  |
|  | 00394A | |